REMARKS

Reconsideration is respectfully requested. Claims 22, 30, 32, 41, 42, 45, 48, 49, 58-66 are pending. Claims 22, 30 and 42 are amended. No new matter has been added as a result of this amendment.

Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Claim Amendments

Claims 22, 30 and 42 have been amended. Support for the amendments is found in page 21, line 15, and page 22, line 26.

Claim Rejections – 35 U.S.C. § 112, ¶ 1

Claims 61, 62, 65 and 66 stand rejected under 35 U.S.C. § 112, ¶ 1, as failing to comply with the written description requirement on the basis that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 22, 30, 32, 41, 42, 45, 48, 49, and 58-66 stand rejected under 35 U.S.C. § 112, ¶ 1, as failing to comply with the written description requirement on the basis that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Particularly, the Examiner asserts that Applicants have provided merely a desire or plan for obtaining a desired result and have failed to provide a precise definition such as by sequence. Applicants respectfully disagree.

A. There is no requirement of providing a precise definition such as by sequence in order to meet the requirement of the written description requirement.

In *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), the Federal Circuit held that "[a] written description of an invention involving a chemical genus, like a description of a

chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Lilly*, at 1405 (citation omitted). The court then addressed the manner by which a genus of cDNAs might be described: "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Lilly*, at 1405.

More recently, in *Capon v. Eshha*, 76 USPQ2d 1078, (Fed. Cir., 2005), the Federal Circuit held that application of a *per se* rule requiring in the specification of a claimed nucleotide sequence is incorrect when the sequence is already known in the filed. This is an interference case appealed from the Board of Appeal and Interferences. The invention at issue were chimeric DNA that encoded single-chain chimeric proteins for expression on the surface of cells of the immune system, plus expression vectors and cells transformed by the chimeric DNA. *Capon*, at 1080. One party in the suit has patent issued; the other party has the claims allowed, one of which reads:

> 1. A chimeric gene comprising
> a first gene segment encoding a single-chain Fv domain (scFv) of a specific antibody and
> a second gene segment encoding partially or entirely the transmembrane and cytoplasmic, and optionally the extracellular, domains of an endogenous protein
> wherein said endogenous protein is expressed on the surface of cells of the immune system and triggers activation and/or proliferation of said cells,
> which chimeric gene, upon transfection to said cells of the immune system, expresses said scFv domain and said domains of said endogenous protein in one single chain on the surface of the transfected cells such that the transfected cells are triggered to activate and/or proliferate and have MHC nonrestricted antibody-type specificity when said expressed scFV domain binds to its antigen.
> *Capon*, at 1880.

In determining the validity of claims including this one, the Board held that the specification does not satisfy the written description requirement because the inventors "claim novel genetic material described in terms of the functional characteristics of the protein it encodes", and "persons having ordinary skill in the art would not have been able to visualize and recognize the identity of the claimed genetic material without considering additional knowledge in the art, performing additional experimentation, and testing to confirm results." *Capon,* at 1082. The Board interprets the controlling precedents "required inclusion in the specification of the complete sequence of 'at least one' chimeric gene." *Capon* , at 1083.

The Federal Circuit disagreed. It held that "the Board erred in ruling that § 112 imposes a *per se* rule requiring in the specification of nucleotide sequence of the claimed DNA, when the sequence is already known in the field." *Capon*, at 1087.

The USPTO further interpreted the written description requirement in "Synopsis of Application of Written Description Guidelines" ("Guidelines"), which provides two examples that are relevant here.

Example 9 of the Guidelines reads:

> An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO:1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity.
> Guidelines, at 35.

The Guidelines concludes the claimed invention in this example meets the written description requirement because a representative number of species is disclosed, and "highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention." Guidelines, at 36-37 (emphasis added).

Example 14 of the Guidelines reads:

> A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A →B.
> Guidelines, at 53.

The Guidelines concludes the claimed invention in this example meets the written description requirement because all members have at least 95% structure identity with the reference compound and "the presence of an assay which applicant provides for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of specified catalytic activity." Guidelines, at 54.

In these examples the partial structure description is homologue to actual sequence, and the function are either the ability to "bind[] to a dopamine receptor and stimulate[] adenylate cyclase activity", or to "catalyze the reaction of A →B." In fact, in *Ex parte Chung* (Appeal NO. 2004-2201, not binding precedent), the Board, in analyzing the above discussed Example 9 of the Guidelines, states that "the Guidelines does not place any restriction as how the coding function of the DNA may be claimed." *Ex parte Chung* , at 6.

Therefore, the controlling cases and the Guidelines support the proposition that there is no need to "provide a precise definition such as by sequence" in order to meet the written description requirement. A composition, such as DNA or protein, can be described by structure description in combination with function description.

B. The instant claims meet the written description requirement because is discloses both structure and function and a correlation between structure and function.

In mapping out the procedure of analyzing claims for written description requirement, the Guidelines provides that the examiner should consider all disclosed distinguishing identifying characteristics such as partial structure, physical and/or chemical properties, known or disclosed correlation between structure and function, method of making, and combination of these factors. Guidelines, at 8. Applicants submit that pending claims meet the written description requirement when analyzed under the Guidelines.

Claims 45, and 59-62 depends on claims 22, which as amended recites a formula comprises a peptide and "wherein upon cleavage of said peptide with a caspase, the T_1 of said MRI agent is changed."

Claims 32, 41, 48, and 63-66 depend on claim 30, which as amended recites a formula comprises a peptide and "said peptide is cleaved with a caspase in said tissue, cell or patient such that the T_1 of said MRI agent is changed."

Claims 48, 49, 58, and 63-66 depend on claim 42, which as amended recites a formula comprises a peptide and "contacting said peptide with a caspase such that upon cleavage of said peptide with said caspase the T_1 value of said MRI agent is changed."

Thus in each of these claims there is a structure described by a formula and functional language that provides distinguishing identifying characteristics of the peptide: it has the chemical properties such that it is cleaved by caspase. The specification discloses that suitable enzyme targets, among others, include caspases such as caspase-3, -5 and -8, other caspases and interleukin converting enzyme (ICE). *See* page 22, lines 19-21. The specification also discloses that the invention explicitly contemplates that when the target substance is a protease, the blocking moiety of the MRI agent can be a peptide capable of being cleaved by the target protease. *See* page 22, line 25, to page 23, line 5. Thus, a skilled artisan would easily understand that when caspases are the target substance to be detected, the peptide in the

claimed invention would comprise a caspase substrate peptide. As set forth in the Amendment and Response to Office Action dated 11/10/2004 and as acknowledged by the Examiner in the Office Action mailed 04/22/2005, peptide substrates for caspase are well known in the art. As art-known caspase substrates, the peptides is to be cleaved with caspase, releasing at least a portion of the peptide to expose a metal coordination site to water and leading to a change in T_1 effect of the MRI agent. Therefore, there is a known and disclosed correlation between the structure, here the peptide, and the function - to be cleaved by caspase.

Because claimed invention is described by structure and function and there is known correlation between the structure and function, Applicants have described and were in possession of the claimed invention. Applicants respectfully request the rejection be withdrawn.

Claim Rejections – 35 U.S.C. § 112, ¶ 2

Claims 30, 32, 41, 48, 63 and 64 stand rejected under 35 U.S.C. § 112, ¶ 2, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Without admitting the propriety of the rejection and reserving the right to pursue the broader claim in continuing applications, claim 30 and hence claims 32, 41, 48, and 63, dependent thereon, have been amended to recite "under conditions whereby said peptide is cleaved with a caspase." Applicants submit that claims 30, 32, 41, 48, 63 and 64 now meet the requirements of § 112, ¶ 2 and request the rejection be withdrawn.

Claim Rejections – 35 U.S.C. § 103

Rejection of Claim 22 over *Gries*

Claim 22 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Gries et al. (U.S. Patent No. 5,648,063)) ("*Gries*"). Applicants respectfully disagree.

When rejecting claims under 35 U.S.C. §103, the Examiner bears the burden of establishing a *prima facie* case of obviousness. *See*, e.g., *In re Bell* 26 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. Section 2142. To establish a *prima facie* case, three basic criteria must be met: (1) the prior art reference(s) must teach or suggest each and every limitation of the rejected claims; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine their teachings; and (3)

there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not in Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); M.P.E.P. §2142.

A. Gries does not teach "upon cleavage of said peptide with a caspase, the T_1 of said MRI agent is changed."

Claim 22 recites a formula comprising a peptide and the limitation "wherein upon cleavage of said peptide with a caspase, the T_1 of said MRI agent is changed."

Gries discloses complex salts for use in NMR, X-ray and/or ultrasonic diagnosis. The complex salts are formed from the anion of a complex acids and one or more central ions. *See* col. 1, lines 21-35. *Gries* also discloses that the complexing acids can be coupled as conjugates with biomolecules that are known to concentrate in the organ or part of the organ to be examined. The biomolecules could be protein or peptides. *See* col. 4, lines 26-49. However, *Gries* does not teach the peptide is cleaved. This is because the function of the peptide in the compound disclosed in *Gries* serves as a targeting moiety to bring the agent to the organs to be examined; cleaving the peptide off the agent would render the compound unsuitable for its intended use. Moreover, *Gries* actually discloses that "the medium according to the invention exhibit not only a great stability in vitro but also an exceptionally great stability in vivo." *See* col. 7, lines 63-66. This suggests the compound is not cleaved.

In addition, *Gries* is directed to a method of diagnosis through the delivery of a physiologically tolerated MRI or X-ray active agent, and a person skilled in the art will understand that the agents as taught by *Gries* are always "on". There is no teaching or suggestion anywhere in *Gries* that the agents can be switched from "off" to "on" by the cleavage of the peptide as the instant invention claims. In the instant invention, after the cleavage of the peptide by caspase the blocking moiety stops occupying at least one coordination site of the metal ion complex when the target substance is present, thereby freeing at least one coordination site of the metal ion such that rapid exchange of water at this site results in a change in the T_1 of the MRI agent.

Therefore, *Gries* fails to teach this limitation of the instant invention.

B. There is no suggestion or motivation in *Greis* to modify *Gries* to reach the instant invention.

If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. MPEP 2143.01.

As presented above, *Gries* is directed to a method of diagnosis through the delivery of a physiologically tolerated MRI or X-ray active agent. *Gries* discloses that complexing acids can be coupled with antibodies such as monoclonal antibodies specific to tumor associate antigens for use in tumor diagnosis. *See* col. 4, lines 31-33. The compounds of conjugated biomolecules taught by *Gries* confer to such agents the property of concentrating the agent in the organ to be examined. *See* col. 4, lines 26-28. The intent use for such agents is to improve the image quality of proton nuclear spin tomography. *See* col. 2, line 42-43. *Gries* never teaches or suggests that the agent can be switch from "off" to "on" by the cleavage of the peptide as the instant invention claims, to indicate whether or not the target enzyme is present. A person skilled in the art will understand that the agents taught by *Gries* are always "on".

If the peptide in *Gries* were modified to have such property, i.e., to be cleaved by caspase, the modification would render the prior art unsatisfactory for its intended purpose. As presented above, the peptide in the compound disclosed in *Gries* serves as a targeting moiety to bring the agent to the organs to be examined. Cleavage of the localization sequence would render it ineffectual.

For this reason, *Gries* does not provide the motivation or suggestion for modifying the disclosed compound to produce a switching mechanism to make the claimed composition.

Because *Gries* does not teach each and every limitation, does not provide suggestion or motivation for modification, the Examiner failed to present a *prima facie* case for obviousness rejection. Applicants therefore request the withdrawal of the rejections.

Rejection of Claims 30, 32, 41, 42, 45, 48, 49 and 58-60 over Greis in view of *Zychlinsky*

Claims 30, 32, 41, 42, 45, 48, 49 and 58-60 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Gries* in view of Zychlinsky (U.S. Patent No. 5,972,899) ("Zychlinsky").

A. There is no suggestion or motivation in either *Greis or Zychlinksy* to modify *Gries* to reach the instant invention.

As presented above, *Gries* does not provide the motivation for modifying the prior art compound to produce a switching mechanism, and there is no suggestion or motivation is present in *Gries* to make the claimed composition. This defect is not cured by *Zychlinsky*.

Zychlinsky is directed to method for inducing apoptosis in a eukaryotic cell by providing to that cell a IpaB encoding DNA. *See* col. 6, lines 46-50. IpaB is able to bind to ICE (caspase-1) to activate a program of apoptosis. *See* col. 3, lines 17-20. It discloses a chimeric protein comprises at a receptor domain capable of binding a selected oligomerizing ligand and a protein domain that, upon oligomerization with one or more like domain, can trigger the transcription of a target gene. *See* col. 17, lines 31-40. It further discloses the purpose to use the oligomerized lingands , such as steroids, is to reduce their natural biological activity when introduced into a patient. *See* col. 20, lines 8-12. Therefore, the disclosure of *Zychlinky* is not related to MRI imaging technology. For this reason, there is no suggestion or motivation provided in *Zychlinksy* to combine it with *Gries* or to modify *Gries* to reach the claimed invention.

B. There is no expectation to success in combining *Gries* with *Zychlinksy*.

As presented above, *Gries* teaches compounds that is stable both in vivo an in vitro and will concentrate in the tissues or organs being examined in order to improve the image quality. Therefore, such compounds are in the "on" status all the time. It cannot be switched from "off" to "on" in order to detect the presence of target enzymes being analyzed, as the instant invention claims. Furthermore, if the peptide in *Gries* were modified to have such property, the modification would render the prior art unsatisfactory for its intended purpose. As presented above, the function of the peptide in the compound disclosed in *Gries* serves as a targeting moiety to bring the agent to the tissues or organs to be examined. Thus, even if an artisan were to combine the caspase taught by *Zychlinsky* with a chelator of *Gries* that was modified, the modified prior art would fail for lacking the ability to localize and harming the patient. For this reason, there is no expectation of success in combining *Gries* with *Zychlinski.*

Because there is no suggestion or motivation to combine *Gries* with *Zychlinsky*, and there is no reasonable expectation of success in combing *Gries* with *Zychlinsky*, the Examiner has not established a *prima facie* case for obviousness and Applicants request the withdrawal of the rejection.

CONCLUSION

Applicants respectfully submit that all pending Claims of the captioned Application satisfy all requirements for patentability and are in condition for allowance. An early indication of the same is therefore respectfully requested.

If the Examiner determines that prosecution of the instant application would benefit from a telephone interview, the Examiner is invited to call the undersigned attorney at (415)-781-1989.

Respectfully submitted,
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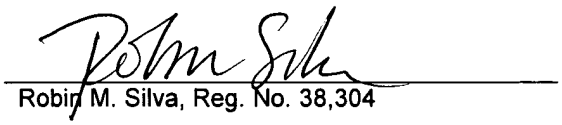
Dated: May 18, 2006 By: 
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Filed under 37 C.F.R. §1.34

4845-2475-1616\25/16/2006 3:03 PM